

## **REMARKS**

Claims 1-10 were pending before the Office. By this amendment, claims 1-10 are amended. Claims 11-19 are new. Accordingly, claims 1-19 shall be pending upon entry of this amendment.

The amendments made herein have been made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications.

Support for the amendments can be found throughout the originally-filed application, including the specification, examples and claims.

No new matter has been added by this amendment.

### ***The objection is overcome***

The Office action objects to claim 9 as being an improper dependent claim for allegedly failing to further limit the claim on which it depends. While the Applicants do not necessarily agree with the objection, claims 8 and 9 have been amended to recite the artificial chaperone limitation only in claim 9.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present objection.

### ***The rejections under 35 USC §102(b) are overcome***

The Office Action rejects claims 1-6 and 8 under 35 USC §102(b) are allegedly being anticipated by Domingues *et al.* (*Journal of Biotechnology*, 84:217-230, 2000)

(“DOMINGUES”). In addition, claims 1, 4-6, 8 and 10 are rejected under 35 USC §102(b) as allegedly being anticipated by Kastelein *et al.* (EP0301835A1) (“KASTELEIN”). Applicants respectfully disagree with the rejections and traverse as follows.

As a first matter, the Examiner is respectfully pointed to M.P.E.P § 2131 which states that “[a] claim is anticipated **only if each and every element** as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *See Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). It will be shown below that DOMINGUES and KASTELEIN, either standing alone or in combination, do not expressly or inherently teach each and every element of the claimed invention, and thus, do not anticipate the present claims.

Turning first to the presently claimed invention, each of the claims specifies a method purifying Interleukin-4 (IL-4) or muteins thereof comprising: expressing the IL-4 or muteins thereof in a prokaryotic cell thereby forming inclusion bodies containing IL-4 or muteins thereof in said prokaryotic cell; disrupting the prokaryotic cell to release the inclusion bodies; separating the inclusion bodies from the cell debris; solubilizing the inclusion bodies in a solution that includes a denaturing agent, thereby denaturing the IL-4 or muteins thereof; separating the denatured IL-4 or muteins thereof using an immobilized metal chelate affinity chromatography (IMAC) system; and releasing the IL-4 or muteins thereof from the IMAC system, thereby obtaining a renatured IL-4 or muteins thereof. The present invention is based, in part, on the surprising discovery that denatured IL-4 is capable of binding to the resin during IMAC, which provides non-native IL-4 after IMAC of about 90% as judged by SDS-PAGE analysis. See page 13, lines 1-16.

Turning now to the references, DOMINGUES reports on a study that examined various approaches to improving the refolding yield of recombinant interleukin-4 without detrimentally altering the activity of the protein. The study focused on reducing the occurrence of undesirable folding intermediates by either replacing exposed hydrophobic residues with polar ones or by stabilizing alpha-helical structures in the protein. DOMINGUES discusses various steps involved in purifying and refolding recombinant interleukin-4 protein. However, it does not teach or suggest each and every of the steps required by the claims. DOMINGUES relates to a method for preparing IL-4 by recombinant expression that involves expressing the IL-4 as inclusion bodies, disrupting the cells, separating out the inclusion bodies, washing the inclusion bodies, solubilizing the inclusion bodies by denaturation, and renaturing the IL-4 protein by ultrafiltration. Unlike the instantly claimed invention, however, DOMINGUES does not teach or suggest or even recognize the step of purifying the denatured IL-4 or muteins thereof with immobilized metal chelate affinity chromatography (IMAC). Indeed, DOMINGUES has nothing to do with IMAC or the purification of proteins involving IMAC. Accordingly, DOMINGUES does not anticipate the instant invention, and thus, this Section 102 rejection should be reconsidered and withdrawn.

KASTELEIN relates to a method for refolding and purifying recombinant interleukin-4 from inclusion bodies from bacterial host cells. KASTELEIN relates to various steps involved in purifying and refolding recombinant interleukin-4 protein, however, it does not teach or suggest each and every of the steps required by the claims. KASTELEIN provides a method involving expressing interleukin-4 in inclusion bodies, disrupting the cells and separating the inclusion bodies, washing the inclusion bodies, solubilizing the inclusion bodies by denaturation,

renaturing the IL-4 by dialysis and purifying the IL-4 product using gel filtration chromatography. Unlike the instantly claimed invention, however, KASTELEIN does not teach or suggest or even recognize the step of purifying the denatured IL-4 or muteins thereof with immobilized metal chelate affinity chromatography (IMAC). And, like DOMINGUES, KASTELEIN has nothing at all to do with IMAC or the purification of proteins involving IMAC. Accordingly, KASTELEIN does not anticipate the instant invention, and thus, this Section 102 rejection should be reconsidered and withdrawn.

*The rejections under 35 USC §103 are overcome*

The Office action rejects claim 7 under 35 U.S.C. §103(a) as being unpatentable over DOMINGUES, as applied to claims 1-6 and 8, and further in view of Apeler et al. (EP1022337A2) (“APELER”). Claim 9 is rejected under 35 U.S.C. §103(a) as being unpatentable over DOMINGUES, as applied to claims 1-6 and 8, and in further view of Gellman et al. (U.S. Patent No. 5,563,057) (“GELLMAN”). Applicants respectfully disagree with the above rejections and traverse as follows.

As the Examiner will appreciate, Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), was recently reaffirmed by KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) as providing the correct analytical framework for determining obviousness. Under Graham, obviousness is a question of law based on underlying factual inquiries that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis. The Office action argues that the

combination of references is proper, suggesting there exists some teaching, suggestion, or motivation in the prior art that would have led the skilled artisan to modify or combine cited prior art to arrive at claimed invention.

Under Graham, when the presently claimed invention is evaluated in view of the scope and content of the prior art, it is readily apparent that the differences between the claimed invention and the prior art are such that the present invention would not have been obvious in view of the cited prior art. In particular, *none* of the cited references, *either alone or in combination*, teach or fairly suggest each and every element required by the claims. As already addressed above relating to the Section 102 rejections, neither DOMINGUES or KASTELEIN, unlike all of the present claims, teach or suggest or even recognize the step of purifying the denatured IL-4 or muteins thereof with immobilized metal chelate affinity chromatography (IMAC). In fact, such a step would have been contrary to the knowledge in art at the time of the invention because, while it was known that native interleukin-4 could bind to IMAC resins (see page 12, lines 30-31 of the published PCT application, WO2004/007549), it would not have been expected that *denatured* interleukin-4 would also have been capable of binding to IMAC resins. Neither APELER or GELLMAN cure the deficiencies of DOMINGUES and KASTELEIN, and thus, none of the references, taken alone or in combination, teach or suggest the present invention. Accordingly, the instantly claimed invention is not obvious in view of DOMINGUES and KASTELEIN in further view of either APELER or GELLMAN. Applicants respectfully request reconsideration and withdrawal of the Section 103 rejections.

## CONCLUSION

In view of the remarks herein, Applicants respectfully request reconsideration and withdrawal of all of the rejections as Applicants believe the application to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

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Respectfully submitted,

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